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EXAMINER
JIANG, SHAOJIA A

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 06/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/092,083	MCCALLISTER ET AL.	
	Examiner	Art Unit	
	Shaojia A. Jiang	1617	

-- The MAILING DATE of this communication appears on the c ver sheet with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-43 is/are pending in the application.

4a) Of the above claim(s) 1-31 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 32-43 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 2-3 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Since applicant has two of originally presented claims numbered 33 and 33, the claims herein have been renumbered in accordance with Rule 126, and the dependency of renumbered dependent claims has been completely changed as well. Thus, the claims herein are now numbered 1-43 instead of 1-42 in the original claims.

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-31 drawn to effervescent compositions comprising a bisphosphonate and other agents herein, classified in class 514, subclass 103 and 108, and class 424, subclass 466 for example.

II. Claims 32-43 drawn to methods of treating osteoporosis and inhibiting bone resorption in a mammal comprising the compositions in Group I, classified in class 514, subclass 103 and 108, and class 424, subclass 466 for example.

Inventions Group I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially

different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). Therefore, the criteria for distinct inventions: (1) the process for using the product as claimed can be practiced with another materially different product. In the instant case, for example, Calcium (another materially different product from the instant claimed compositions) can be used in the methods of treating osteoporosis and inhibiting bone resorption in a mammal.

Thus, the search for these inventions would place an undue burden on the Office.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

During a telephone conversation with Mr. Robert W. Hahl on June 12, 2003 a provisional election was made with traverse to prosecute the invention of Group II, claims 32-43. Affirmation of this election must be made by applicant in replying to this Office action.

Thus, Claims 1-31 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim

remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claims 32-43 are examined on the merits herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 32-43 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: the composition in claims 1 and the composition in claim 26 and the composition in claim 30.

Note that both claims 1, 26 and 30 are withdrawn from further consideration. Insertion of the recitation of compositions of claims 1, 26 and 30 into claims 32, 36, and 40, respectively, would be favorably considered.

In order to expedite prosecution, claims 32-43 will be examined by inserting the recitation of compositions of claims 1, 26 and 30 into claims 32, 36, and 40, respectively, as have apparently been intended.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make

and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 32-43 are rejected under 35 U.S.C. 112, first paragraph, for scope of enablement because the specification, while being enabling for co-administering to a mammal a bisphosphonate with the particular acid component disclosed in the specification at page 7 lines 1-5, and the particular alkaline effervescing component disclosed in the specification at page 7 [0027], and/or co-administering the particular anti-ulcer agent disclosed in the specification at page 3 [0008] in the claimed methods herein, does not reasonably provide enablement for co-administering to a mammal a bisphosphonate with any acid component and any alkaline effervescing component, and further in combination with any anti-ulcer agent employed in the claimed methods of the particular treatments herein, i.e., treating osteoporosis and inhibiting bone resorption in a mammal.

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without ***undue experimentation***. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

The nature of the invention: The instant invention pertains to methods of treating osteoporosis and inhibiting bone resorption in a mammal.

The relative skill of those in the art: The relative skill of those in the art is high.

The breadth of the claims: The instant claims 32-43 are deemed very broad since these claims reads on any acid components and any alkaline effervescing components, and any anti-ulcer agents employed in the claimed methods of treatment herein.

The amount of direction or guidance presented:

Functional language at the point of novelty, as herein employed by Applicants in claims 1-2, is admonished in *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398 (CAFC, 1997). The CAFC clearly states that "[A] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials" at 1405(emphasis added), and that "It does not define any structural features commonly possessed by members of the genus that distinguish from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus.." at 1406 (emphasis added).

In the instant case, "an acid component" and "an alkaline effervescing component", and "an anti-ulcer agent", recited in the instant claims are purely functional distinction. Hence, these functional recitations read on any compounds that might have the recited functions. However, the specification merely provides those particular

compounds for each kind of functional compounds for the claimed method of treatment herein.

Thus, Applicants functional language at the points of novelty in claims 1-2 fails to meet the requirements set forth under 35 U.S.C. 112, first paragraph.

The predictability or unpredictability: the instant claimed invention is highly *unpredictable* as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art cannot fully described genus, visualize or recognize the identity of the members of the genus, by structure, formula, or chemical name, of the claimed subject matter, except those particular compounds of formula disclosed in the specification, as discussed above in *University of California v. Eli Lilly and Co.* Hence, in the absence of fully recognizing the identity of the members genus herein, one of skill in the art would be unable to fully predict possible physiological activities of any compounds having claimed functional properties in the claimed method of treatment herein.

Moreover, one of skill in the art would recognize that it is highly unpredictable in regard to therapeutic effects for treating osteoporosis and inhibiting bone resorption in a mammal, side effects, and especially serious toxicity that may be generated by drug-drug interactions when and/or after administering to a host (e.g., a postmenopausal

woman) the *combination* of a bisphosphonate with any compounds represented by "an acid component" and "an alkaline effervescing component", and "an anti-ulcer agent", and/or while the patient also administering other medicines. See text book "Goodman & Gilman's The Pharmacological Basis of Therapeutics" regarding possible drug-drug interactions (9th ed, 1996) page 51 in particular. This book teaches that "The frequency of significant beneficial or adverse drug interactions is unknown" (see the bottom of the left column of page 51) and that "Recognition of beneficial effects and recognition of and prevention of adverse drug interactions require a thorough knowledge of the intended and possible effects of drugs that are prescribed" and that "The most important adverse drug-drug interactions occur with drugs that have serious toxicity and a low therapeutic index, such that relatively small changes in drug level can have significant adverse consequences" (see the right column of page 51) (emphases added).

In the instant case, in the absence of fully recognizing the identity of the members genus herein except those particular compounds of each kind in the specification, one of skill in the art would not be unable to fully predict the possible treatments herein and possible adverse effects occurring with many compounds having claimed functional properties and their combinations to be administered to a host in the claimed methods herein. Thus, the teachings of the "Goodman & Gilman's" book clearly support that the instant claimed invention is highly unpredictable.

The presence or absence of working examples and the quantity of experimentation necessary:

It is noted that Examples 1-6 in the specification merely provide several particular compounds of each kind herein in combination with a bisphosphonate (see page 14-19).

Thus, the specification fails to provide clear and convincing evidence in sufficient support of the broad use of a bisphosphonate in combination with any compounds having those functions recited in the instant claims. As a result, necessitating one of skill to perform an exhaustive search for the embodiments of any compounds having those functions recited in the instant claims suitable to practice the claimed invention.

Genentech, 108 F.3d at 1366, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the *Wands* factors, the case *University of California v. Eli Lilly and Co.* (CAFC, 1997) and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in *undue experimentation* to test all compounds encompassed in the instant claims and their combinations to be administered to a host employed in the claimed methods of the particular treatments herein, with no assurance of success.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 32-35 are rejected under 35 U.S.C. 102(b) as being anticipated by Katdare et al. (5,853,759, PTO-1449 submitted March 8, 2002).

Katdare et al. discloses that bisphosphonates including instant preferred bisphosphonates are known to have utility as pharmaceutical agents for inhibiting bone resorption (see col.1 lines 14-42). Katdare et al. particularly discloses that a composition be administered orally comprising the instant preferred bisphosphonate, alendronate, is known to be useful in a method of treating osteoporosis in postmenopausal women (human mammals) (see col.1 lines 43-49). The disclosed pharmaceutical effervescent formulations of alendronate therein in tablet and powders which are placed in an convenient amount of water to produce effervescent liquid (solution), and that the patient drinks the effervescent solution, are for eliminating or minimizing side effects during the medication (i.e., for treating osteoporosis and/or inhibiting bone resorption in a mammal) (see col.1 lines 8-11 and 48-57, col.2 lines 63-67). The particular disclosed alendronate effervescent composition of Katdare et al. in Example 1 comprises alendronate in an effective amount (known for treating osteoporosis and/or inhibiting bone resorption), the instant preferred acid component, citric acid, and the instant preferred alkaline effervescing component, sodium bicarbonate and sodium carbonate, flavoring agent or sweetener and color agent, and then an convenient amount of water added to produce effervescent solution to be administered orally (see Example 1 at col.4 line 34-35 and 46-56 in particular), and the composition also comprises a lubricant

such as sodium benzonate and polyethylene glycol (PEG) (also known as a solubilizing agent) (see col.2 lines 24-26 and col.4 lines 21-33).

Regarding the inherent property, the pH of the solution, it is noted that citric acid is employed in an excess in the composition therein to efficiently generate the effervescence and to sequester any ions to complex with alendronate, and to enhance favor as well, disclosed by Katdare et al. (see col.3 lines 60-65). Thus, the solution therein is acidic. The pKa of citric acid (known to used as a buffer), pK_1, K_2, K_3 are 3.128, 4.761, and 6.396, respectively (provided by Bull "An Introduction to Physical Biochemistry" page 103, PTO-892). Thus, one of ordinary skill in the art would clearly recognize that the pH values in citric acid buffered solutions are within the instant claim about 3 to about 6.5.

The pH value of the particular alendronate composition in Example 1 is also within the instant claim about 3 to about 6.5, as shown in the calculation below:

Example I discloses that citric acid is 650 mg and the molecular weight (or formula weight, FW) of citric acid is 192.12 (provided by Aldrich Handbook page 436, PTO-892). Thus, the moles of citric acid is 650 ÷ 192.12 =3.38 mmol.

Example I discloses that sodium bicarbonate is 367 mg and the molecular weight of sodium bicarbonate is 84.01 (provided by Aldrich Handbook page 1505, PTO-892). Thus, the moles of sodium bicarbonate is 367 ÷ 84.01= 4.37 mmol.

Example I discloses that sodium carbonate is 40 mg and the molecular weight of sodium carbonate is 105.99 (provided Aldrich Handbook page 1498, PTO-892). Thus, the moles of sodium carbonate is 40 ÷ 105.99 =0.38 mmol.

It is known in the basic chemistry that the mole ratio of citric acid to sodium carbonate for neutralizing citric acid by sodium carbonate (or known as equal equivalent) is 2:3 (see col.3 line 67 to col.4 line 1) and the mole ratio of citric acid to sodium bicarbonate for neutralizing citric acid by sodium bicarbonate is 1:3.

Thus, 4.37 mmol of sodium bicarbonate neutralizes 4.37 X 1/3 = 1.46 mmol of citric acid;

2.65 mmol of sodium carbonate neutralizes 0.38 X 2/3 = 0.25 mmol of citric acid;

Therefore, the left or excess of citric acid in the solution

= 3.38 – (1.46 +0.25) =1.67 mmol.

Therefore, 1.67 mmol, about a half amount of citric acid is free and left in the solution. Thus, the solution is acidic. As discussed above, according the known pKa values of citric acid, the pH value of the effervescent composition of Example 1 is within the instant claim about 3 to about 6.5.

Moreover, after administering of the effervescent solution of Katdare et al., the pH of the mammal's stormach would be inherently raised to about 3 since the pH of the solution is about 3 to 6.5 and the citric acid solution is a known buffered solution which would mediate the pH in the mammal's stomach for a period of time.

Thus, oral administration of Kuznicki's effervescent composition to a mammal is useful in methods of treating osteoporosis and inhibiting bone resorption. Therefore, the disclosure of Katdare et al. anticipates claims 32-35.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 32-39 are rejected under 35 U.S.C. 102(b) as being anticipated by Daifotis et al. (5,994,329, PTO-1449 submitted March 8, 2002).

Daifotis et al. discloses the compositions of a bisphosphonate comprising a bisphosphonate including instant preferred bisphosphonates such as alendronate, in oral forms therein such as in effervescent compositions, and also comprising solubilizing agents such as polyvivylpyrrolidone, coloring agents, and sweeteners (see col.1 lines 15-58, col.11 line 55 to col.12 lines 3, col.12 lines 3-34), especially the liquid formulation or composition of Example 8 employed in the methods of treatments herein in Examples 2-6 comprising alendronate salt, the instant preferred acid component, citric acid, and the alkaline component such as sodium citrate, and sodium hydroxide which is used to adjust the pH of the solution formulation to 6.75 (reads on the instant claim, about 6.5)(see particular Example 8 at col. 19 lines 40-62,). These compositions of a bisphosphonate be administered orally are useful for methods of treating osteoporosis and bone resorption in human mammals such as postmenopausal women (see also abstract, col.5 lines 21-23 and 29-35, col.7 lines 31-37, and Examples 2-6 at col.17-18).

Daifotis et al. further discloses that the methods and bisphosphonate compositions therein also comprise a histamine H2 receptor blocker (H2-antagoinsts),

e.g., cimetidine, famotidin, and nizatidine, which are the instant preferred anti-ulcer agents, in order to minimize adverse gastrointestinal effects produced by a bisphosphonate (see col.13 lines 21-46).

Moreover, after administering of the liquid composition of Example 8 in Daifotis et al., the pH of the mammal's stormach would be inherently raised to about 3 since the pH of the solution is 6.75 and the citric acid solution is a known buffered solution which would mediate the pH in the mammal's stomach for a period of time.

Therefore, the disclosure of Daifotis et al. anticipates claims 32-39.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 40-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Katdare et al. (5,853,759, PTO-1449 submitted March 8, 2002) and Daifotis et al. (5,994,329, PTO-1449 submitted March 8, 2002) in view of Samejima et al. 4,462,982, PTO-1449 submitted March 8, 2002).

The same disclosure of Katdare et al. has been discussed above (see supra at page 10-12).

The same disclosure of Daifotis et al. has been discussed above (see supra at page 13-14).

Katdare et al. and Daifotis et al. do not expressly disclose that bisphosphonate is in a microencapsulated form.

Samejima et al. discloses that microencapsulating active agent(s) is known having advantages in better release control of active agent(s), e.g., rapidly releasing the active in stomach (see abstract and col.1 lines 5-22).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to prepare the bisphosphonate in a microencapsulated form.

One having ordinary skill in the art at the time the invention was made would have been motivated to prepare the bisphosphonate in a microencapsulated form since microencapsulating active agent(s) is known in better release control of active agent(s), e.g., rapidly releasing the active in stomach according to Samejima et al. Therefore, one of ordinary skill in the art would have reasonably expected that a microencapsulated bisphosphonate would improve teh release of a bisphosphonate to reduce adverse gastrointestinal effects produced by a bisphosphonate .

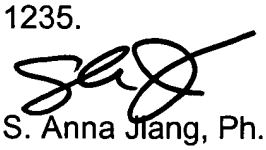
Thus the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

In view of the rejections to the pending claims set forth above, no claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Jiang, whose telephone number is (703) 305-1008. The examiner can normally be reached on Monday-Friday from 9:00 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, Ph.D., can be reached on (703) 305-1877. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-1235.



S. Anna Jiang, Ph.D.
Patent Examiner, AU 1617
June 13, 2003